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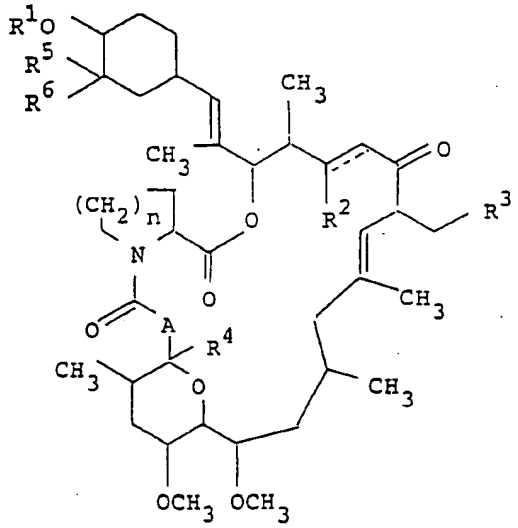
(54) Title: TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME



(I)

(57) Abstract

Compounds of formula (I) are disclosed, wherein R^1 is hydrogen or acyl, R^2 is hydrogen, hydroxy, alkoxy or acyloxy, R^3 is (C_3-C_7)alkyl, aryl(C_2-C_7)alkyl, protected carboxy(C_2-C_7)alkyl, 1-(C_3-C_7)alkenyl, aryl-1-(C_2-C_7)alkenyl or protected carboxy-1-(C_2-C_7)alkenyl, R^4 is hydroxy or alkoxy, R^5 is hydrogen and R^6 is hydroxy or methoxy, or R^5 and R^6 are combined to form oxo, A is methylene, hydroxymethylene or carbonyl, n is an integer of 1 or 2, and the symbol of a line and dotted line is a single bond or a double bond and salts thereof. And processes for their production, and pharmaceutical compositions containing them are also described.

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DESCRIPTION

TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

This invention relates to novel tricyclo compounds having pharmacological activities, to a process for their production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel tricyclo compounds, which have pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof as a medicament.

Accordingly, one object of this invention is to provide the novel tricyclo compounds, which are useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

Another object of this invention is to provide a process for production of the tricyclo compounds by synthetic process.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the tricyclo compounds.

Still further object of this invention is to provide a use of the tricyclo compounds as a medicament for

treating and preventing resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

European Patent Application 184162 (Fujisawa Pharmaceutical Co. Ltd.) discloses a number of macrocyclic compounds isolated from microorganisms belonging to genus Streptomyces such as Streptomyces tsukubaensis No. 9993 (FERM BP-927) and Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 (FERM BP-928). Such macrolides are particularly numbered FR-900506, FR-900520, FR-900523 and FR-900525. And the preparation of some their derivatives is also described.

International Patent Application WO 89/05304, European Patent Application Nos. 353678, 349049, 349061, 356399, 402931, etc also disclose a number of macrocyclic immunosuppressive compounds.

We have now found a novel group of compounds which possess certain advantageous properties over those disclosed previously.

Thus, according to the invention, we provide a new compound of the following formula:

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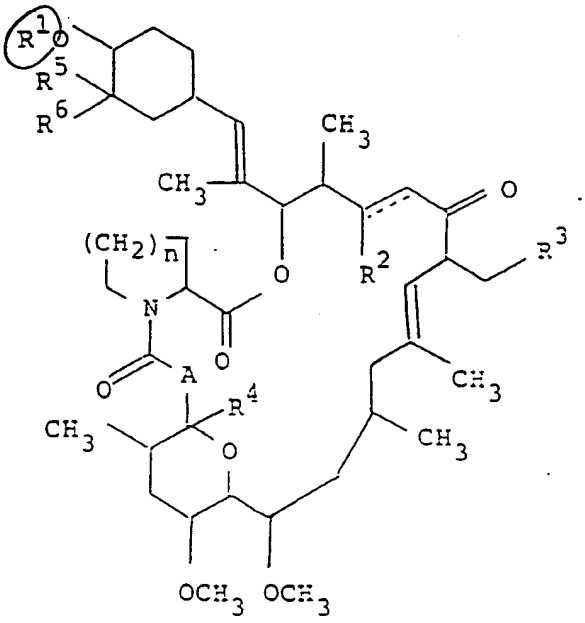


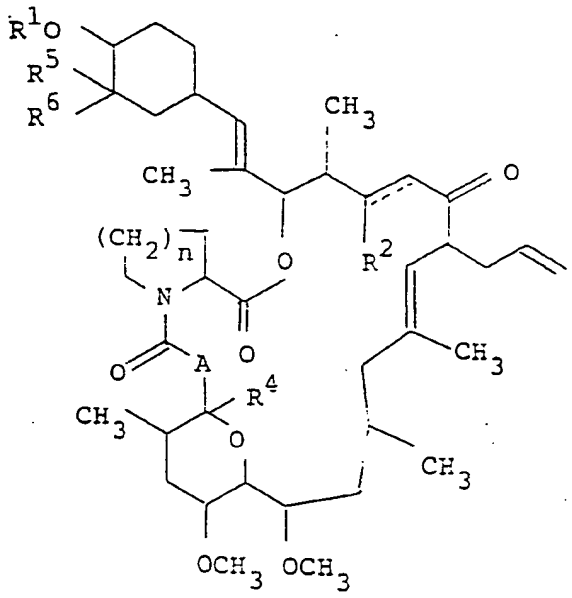
(I)

wherein R^1 is hydrogen or acyl,
R^2 is hydrogen, hydroxy, alkoxy or acyloxy,
R^3 is (C_3-C_7)alkyl, aryl(C_2-C_7)alkyl, protected carboxy(C_2-C_7)alkyl, 1-(C_3-C_7)alkenyl, aryl-1-(C_2-C_7)alkenyl or protected carboxy-1-(C_2-C_7)alkenyl,
R^4 is hydroxy or alkoxy,
R^5 is hydrogen and R^6 is hydroxy or methoxy, or
R^5 and R^6 are combined to form oxo,
A is methylene, hydroxymethylene or carbonyl,
n is an integer of 1 or 2, and
the symbol of a line and dotted line is a single bond or a double bond.

With respect to the tricyclo compounds (I) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

According to this invention, the object tricyclo compounds (I) can be prepared by the following processes.

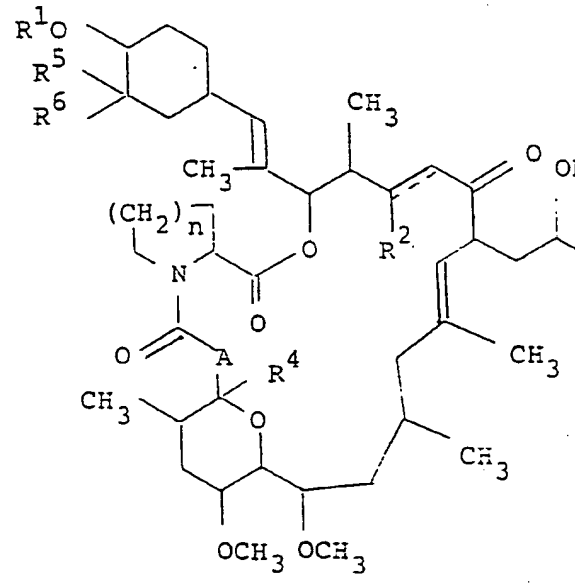
Process 1



(II)

or a salt thereof

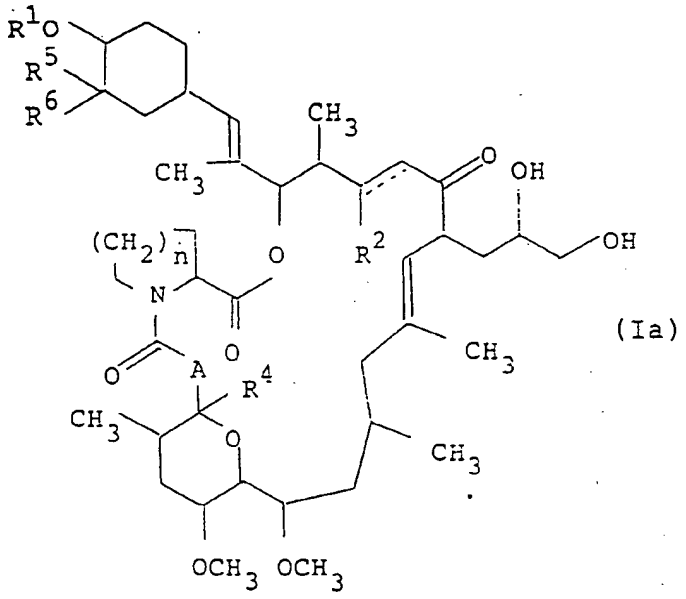
↓ Hydroxylation



(Ia)

or a salt thereof

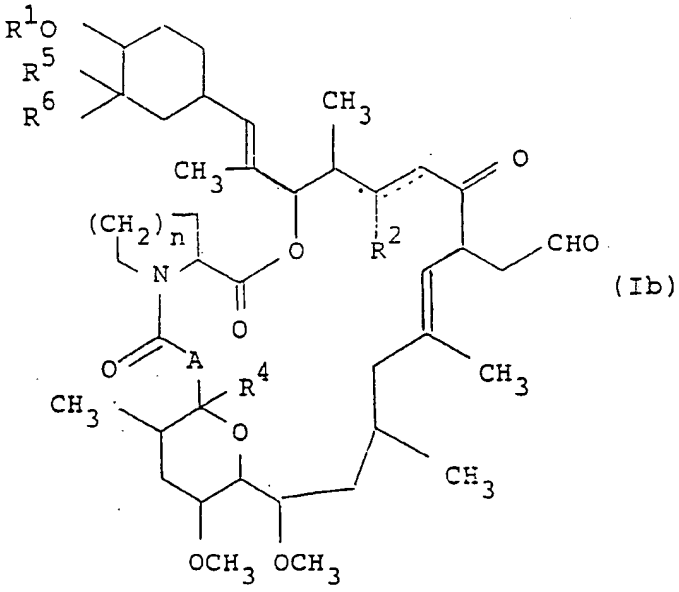
Process 2



(Ia)

or a salt thereof

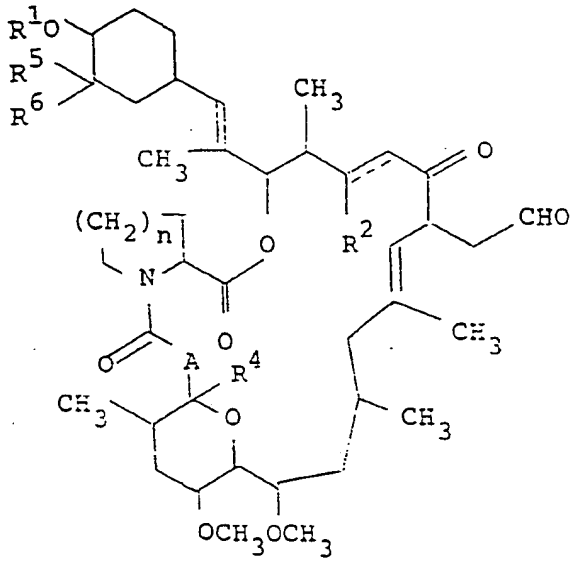
Oxidation



(Ib)

or a salt thereof

Process 3

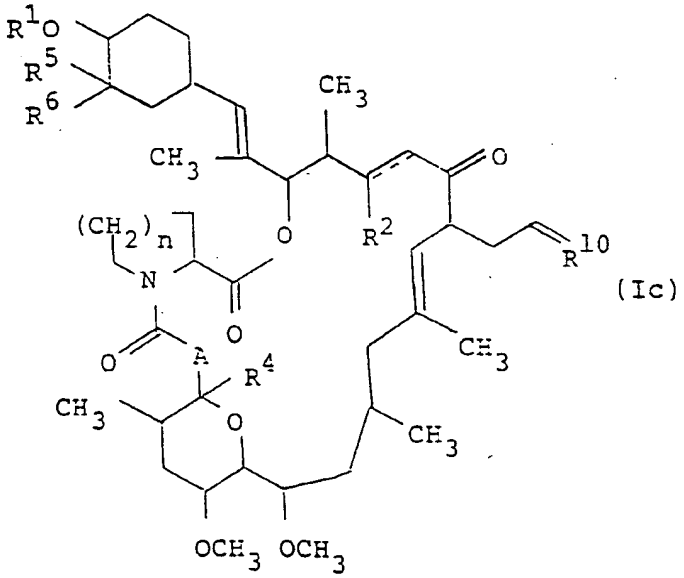


(Ib)

or a salt thereof

$(R^8)_3\overset{\oplus}{P}-R^7\ X^{\ominus}$ (IIIa) or

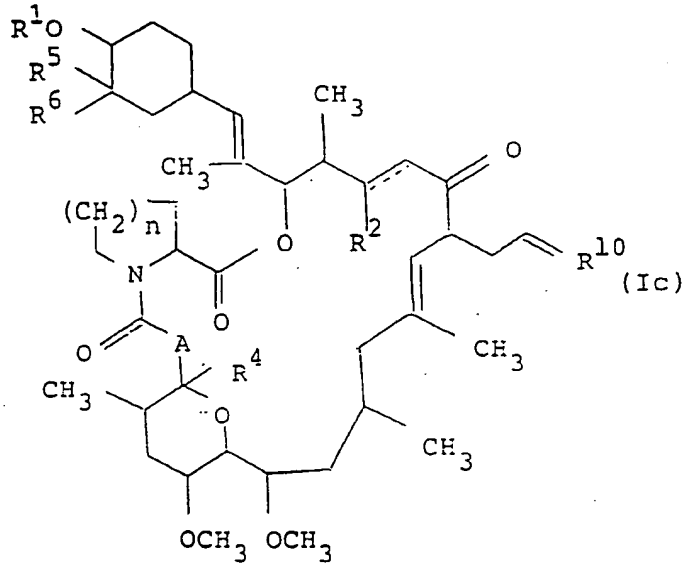
$(R^8)_3P=CH-R^9$ (IIIb)



(Ic)

or a salt thereof

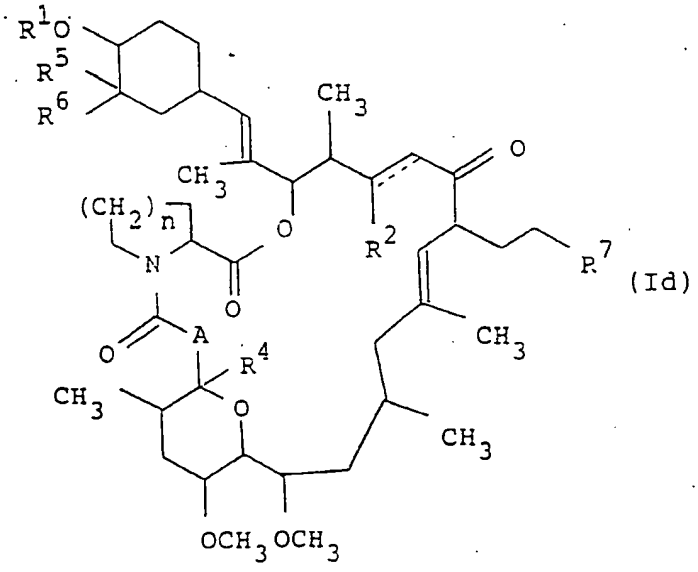
Process 4



(Ic)

or a salt thereof

Reduction



(Id)

or a salt thereof

in which R^1, R^2, R^3, R^4, R^5, R^6, A and n are each as defined above,

R^7 is (C_2-C_6)alkyl, aryl(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl,

R^8 is aryl,

R^9 is protected carboxy,

R^{10} is (C_2-C_6)alkylidene, aryl(C_1-C_6)alkylidene or protected carboxy(C_1-C_6)alkylidene, and

X is halogen.

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "acyl" and acyl group in the "acyloxy" may include aliphatic acyl, aromatic acyl and aliphatic acyl substituted with aromatic group, which are derived from carboxylic, sulfonic and carbamic acids; and the like.

The aliphatic acyl may include lower alkanoyl which may have one or more suitable substituent(s) such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkyloxy(lower)-alkanoyl which may have one or more suitable substituent(s) such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxyheptanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl having one or more

suitable substituent(s) such as carboxy, protected carboxy and hydroxy for example, carboxy(lower)alkylcarbamoyl (e.g. carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), protected carboxy(lower)alkylcarbamoyl such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl (e.g. trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.), hydroxy(lower)alkylcarbamoyl (e.g. hydroxymethylcarbamoyl, hydroxyethylcarbamoyl, hydroxypropylcarbamoyl, hydroxybutylcarbamoyl, hydroxypentylcarbamoyl, hydroxyhexylcarbamoyl, etc.), and the like.

The aromatic acyl may include aroyl which may have one or more suitable substituent(s) such as nitro (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.), arenesulfonyl which may have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), arylcarbamoyl which may have one or more suitable substituent(s) such as halogen (e.g. phenylcarbamoyl, fluorophenylcarbamoyl, chlorophenylcarbamoyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic carbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, morpholinocarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and the like.

The more preferred acyl group thus defined may be C_1-C_4alkanoyl which may have carboxy, cyclo(C_5-C_6)-alkyloxy(C_1-C_4)alkanoyl having two (C_1-C_4)alkyl groups on the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1-C_4)-alkylcarbamoyl, hydroxy(C_1-C_4)alkylcarbamoyl, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl(C_1-C_4)alkyl-carbamoyl, haloarylcarbamoyl, benzoyl which may have one or two nitro, benzenesulfonyl having halogen, phenyl(C_1-C_4)alkanoyl having C_1-C_4alkoxy and trihalo(C_1-C_4)alkyl, morpholinocarbonyl, and the most preferred one may be acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, hydroxypropylcarbamoyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, phenylcarbamoyl, fluorophenylcarbamoyl, chlorophenylcarbamoyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and morpholinocarbonyl.

Suitable alkoxy may be lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy and the like, in which the preferred one is C_1-C_4alkoxy.

Suitable "(C_3-C_7)alkyl" may include straight or branched one such as propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and the like, in which more preferred example may be (C_3-C_5)alkyl and

the most preferred one may be propyl and pentyl.

Suitable "(C_2-C_6)alkyl" may include straight or branched one such as ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, and the like, in which more preferred example may be (C_2-C_4)alkyl and the most preferred one may be ethyl and butyl.

Suitable "aryl(C_2-C_7)alkyl" may include aforementioned (C_3-C_7)alkyl and ethyl, which are substituted with aryl as mentioned below, wherein more preferred example may be phenyl(C_2-C_4)alkyl and the most preferred one may be 2-phenylethyl.

Suitable "protected carboxy(C_2-C_7)alkyl" may include aforementioned (C_3-C_7)alkyl and ethyl, which is substituted with protected carboxy as mentioned below, wherein more preferred example may be (C_1-C_4)alkoxycarbonyl(C_2-C_4)alkyl and the most preferred one may be 2-methoxycarbonylethyl.

Suitable "1-(C_3-C_7)alkenyl" may include straight or branched one such as 1-propenyl, 1-isopropenyl, 1-butenyl, 1-isobutenyl, 1-pentenyl, 1-isopentenyl, 1-neopentenyl, 1-hexenyl, 1-heptenyl, and the like, in which more preferred example may be 1-(C_3-C_5)alkenyl and the most preferred one may be 1-propenyl and 1-pentenyl.

Suitable "aryl-1-(C_2-C_7)alkenyl" may include aforementioned 1-(C_3-C_7)alkenyl and ethenyl, which are substituted with aryl as mentioned below, wherein more preferred example may be phenyl-1-(C_2-C_4)alkenyl and the most preferred one may be 2-phenylethenyl.

Suitable "protected carboxy-1-(C_2-C_7)alkenyl" may include aforementioned 1-(C_3-C_7)alkenyl and ethenyl, which

is substituted with protected carboxy as mentioned below, wherein more preferred example may be (C_1-C_4)alkoxycarbonyl-1-(C_2-C_4)alkenyl and the most preferred one may be 2-methoxycarbonylethenyl.

Suitable "aryl(C_1-C_6)alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, and the like, which is substituted with aryl as mentioned below, wherein more preferred example may be phenyl(C_1-C_4)alkyl and the most preferred one may be benzyl.

Suitable "protected carboxy(C_1-C_6)alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, and the like, which is substituted with protected carboxy as mentioned below, wherein more preferred example may be (C_1-C_4)alkoxycarbonyl(C_1-C_4)alkyl.

Suitable "(C_2-C_6)alkylidene" may include straight or branched one such as ethylidene, propylidene, isopropylidene, butylidene, pentylidene, hexylidene, and the like in which more preferred example may be (C_2-C_4)alkylidene and the most preferred one may be ethylidene and butylidene.

Suitable "aryl(C_1-C_6)alkylidene" may include aforementioned (C_2-C_6)alkylidene and methylene, which are substituted with aryl as mentioned below, wherein more preferred example may be phenyl(C_1-C_4)alkylidene and the most preferred one may be benzylidene.

Suitable "protected carboxy(C_1-C_6)alkylidene" may include aforementioned (C_2-C_6)alkylidene and methylene, which are substituted with protected carboxy as mentioned below, wherein more preferred example may be

(C_1-C_4)alkoxycarbonyl(C_1-C_4)alkylidene and the most preferred one may be methoxycarbonylmethylene.

Suitable "leaving group" may include an acid residue and the like, and suitable examples of "acid residue" may be halogen (e.g. chlorine, bromine, iodine, etc.), sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Suitable "protected carboxy" may include esterified carboxy such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), mono(or di or tri)phenyl(lower)alkoxycarbonyl which may have a nitro group (e.g. benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, etc.), and the like, in which more preferred example may be C_1-C_4 alkoxycarbonyl and the most preferred one may be methoxycarbonyl.

Suitable "aryl" may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like, in which the preferred example may be phenyl.

Suitable "halogen" may be chlorine bromine, fluorine and iodine, in which the preferred one may be chlorine and bromine.

The processes for production of tricyclo compounds (I) of this invention are explained in detail in the following.

Process 1 :

The compound (Ia) or a salt thereof can be prepared

by hydroxylating the compound (II) or a salt thereof.

The hydroxylating agent applicable to this process may be a conventional one which is capable of introducing hydroxy group(s) into the allyl moiety of starting compound (II), for example, alkali metal permanganate (e.g. potassium permanganate, etc.), osmium tetroxide optionally in the presence of a suitable oxidizing agent to regenerate osmium tetroxide (e.g. N-methylmorpholine N-oxide, sodium chlorate, etc.), hydrogen peroxide, and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, pyridine, ethyl acetate, N,N-dimethylformamide, dichloromethane, ethyl ether, isopropyl ether, 1,4-dioxane or a mixture thereof.

The reaction temperature of this reaction is not critical and the reaction is usually conducted under from cooling to warming.

Process 2 :

The compound (Ib) or a salt thereof can be prepared by oxidizing the compound (Ia) or a salt thereof to an aldehyde.

The oxidizing agent applicable to this process may be a conventional one which is capable of oxidizing vicinal diols to an aldehyde, for example, perhalogenic acid or a salt thereof (e.g. periodic acid, sodium metaperiodate, etc.), lead tetra(lower alkanoate) (e.g. lead tetraacetate, etc.), and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, pyridine, ethyl acetate, N,N-dimethylformamide, dichloromethane, ethyl ether, isopropyl ether, 1,4-dioxane, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under from cooling to warming.

Process 3 :

The compound (Ic) or a salt thereof can be prepared by reacting the compound (Ib) or a salt thereof with the compound (IIIa) or (IIIb).

In case that the compound (IIIa) is used in this reaction, this reaction can preferably be carried out in the presence of an organic or inorganic base such as lower alkylalkalimetal (e.g. methyllithium, butyllithium, etc.), alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal hydrogen carbonate (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-N,N-dimethylaminopyridine, etc.), quinoline, and the like.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, benzene, N,N-dimethylformamide, hexane, ethyl ether, isopropyl ether, 1,4-dioxane, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under from cooling to warming.

Process 4 :

The compound (Id) or a salt thereof can be prepared by reducing the compound (Ic) or a salt thereof.

The reduction method applicable for this reaction is a conventional one which is capable of hydrogenating olefinic bond and may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, sulfuric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, palladium hydroxide on carbon, etc.), nickel catalysts (e.g. reduced nikel, nickel oxide, Raney nickel, etc.), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.); rhodium on alumina powder, sodium borohydride, a combination of tri(lower)alkylborane and sodium borohydride, diisobutylaluminum hydride, and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, acetate buffer, etc.), benzene, toluene, xylene, and the like, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The object tricyclo compounds (I) obtained according to the processes as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

Suitable salts of the compounds (I), (Ia), (Ib), (Ic), (Id) and (II) may include pharmaceutically acceptable salts such as basic salts, for example, alkali metal salt (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), ammonium salt, amine salt (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and other conventional organic salts.

With respect to the tricyclo compounds (II) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

The starting compound (II) in the process mentioned above contains known and novel compounds, and the known

compounds are disclosed, for example, in European Patent Publication Nos. 184162 and 323042 and the new compound can be prepared by a conventional manner.

PHARMACOLOGICAL ACTIVITIES OF THE TRICYCLO COMPOUNDS

The tricyclo compounds (I) possess pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, and therefore are useful for the treatment and prevention of immune-mediated diseases controlled by a immunosuppressant such as the resistance by transplantation of organs or tissue such as heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nervus, etc.; graft-versus-host diseases by medulla ossium transplantation; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, and the like; and further infectious diseases caused by pathogenic microorganisms.

Further, the tricyclo compounds (I) are also useful for the treatment and the prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne and Alopecia areata;
various eye diseases such as autoimmune diseases and so on (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae,

corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' ophthalmopathy, etc.);
reversible obstructive airways disease, which includes conditions such as asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness), bronchitis and the like;
inflammation of mucosa and blood vessels such as gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, intestinal lesions associated with thermal burns, leukotriene B_4-mediated diseases;
intestinal inflammations/allergies such as Coeliac disease, proctitis, eosnophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis;
food related allergic diseases which have symptomatic manifestation remote from the gastro-intestinal tract, for example migraine, rhinitis and eczema;
renal diseases selected from interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy;
nervous diseases selected from multiple myositis, Guillain-Barré syndrome, Ménière's disease and radiculopathy;
endocrine diseases selected from hyperthyroidism and Basedow's disease;
hematic diseases selected from pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia;
bone diseases such as osteoporosis;
respiratory diseases selected from sarcoidosis, fibroid lung and idiopathic interstitial pneumonia;

skin diseases selected from dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma;
circulatory diseases selected from arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis;
collagen diseases selected from scleroderma, Wegener's granuloma and Sjogren's syndrome;
adiposis;
eosinophilic fasciitis;
periodontal disease;
nephrotic syndrome such as glomerulonephritis;
hemolytic-uremic syndrome;
photoallergic sensitivity;
male pattern alopecia or alopecia senilis; and so on.

And further, the tricyclo compounds (I) have liver regenerating activity and/or activities of stimulating hypertrophy and hyperplasia of hepatocytes. Therefore, they are useful for the treatment and prevention of hepatic diseases such as immunogenic diseases (e.g. chronic autoimmune liver diseases selected from the group consisting of autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis and cirrhosis.

And further, the tricyclo compounds (I) are useful for various diseases because of its useful pharmaceutical activity such as augmenting activity of chemotherapeutic effect.

As examples for showing such pharmacological activities, the pharmacological test data of the tricyclo compounds (I) is illustrated in the following.

Test 1

Suppression of in vitro Mixed Lymphocyte Reaction (MLR)

The MLR test was performed in microtiter plates, with each well containing 5×10^5 C57BL/6 responder cells ($H\text{-}2^b$), 5×10^5 mitomycin C treated (25 µg/ml mitomycin C at 37°C for 30 minutes and washed three times with RPMI 1640 medium) BALB/C stimulator cells ($H\text{-}2^d$) in 0.2 ml RPMI 1640 medium supplemented with 10% fetal calf serum, 2mM sodium bicarbonate, penicillin (50 unit/ml) and streptomycin (50 µg/ml). The cells were incubated at 37°C in humidified atmosphere of 5% carbon dioxide and 95% of air for 68 hours and pulsed with ^{3}H-thymidine (0.5 µCi) 4 hours before the cells were collected. The object compound of this invention were dissolved in ethanol and further diluted in RPMI 1640 medium and added to the cultures to give final concentrations of 100 nM or less.

The IC_{50} value (mol concentration to suppress 50% of MLR) was calculated by a conventional method, which is shown in the following Table 1.

Table 1 : IC_{50} Value of MLR test on tricyclo compounds (I)

Test compound	IC_{50} value (mol/liter)
tricyclo compound prepared in Example 9	4.1×10^{-9}

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclo compounds (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or

parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops lotion, gel, creme and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used. Particularly, as a solubilizing agent, there may be exemplified water-soluble cellulose polymer (i.e. hydroxypropyl methylcellulose, etc.), water-soluble glycol (i.e. propylene glycol, etc.), etc. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying this composition to human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tricyclo compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

The following examples are given for the purpose of illustrating the present invention.

Example 1

A solution of 17-Allyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (2.57 g) in a mixture of 1,4-dioxane (40 ml) and water (4 ml) was treated with catalytic amount of osmium tetroxide in tetrahydrofuran and 4-methylmorpholine N-oxide (1.15 g), and stirring was continued for 5.5 hours at room temperature. To this reaction mixture was added water, and the separated aqueous phase was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography to give pure 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (1.91 g).

FAB MS : m/z 844 (M + Na)

Example 2

To a solution of 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxy-propyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (220 mg) in 1,4-dioxane (7 ml) was added a solution of sodium metaperiodate (573 mg) in water (2 ml) at 0°C. After 1 hour at the same temperature, diethyl ether and water was added, and the separated aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-

azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (220 mg). This product was used to the next reaction without further purification.

^{1}H NMR ($CDCl_3$) : 9.70-9.78 (1H, m)

Example 3-1)

To a stirred suspension of n-butyltriphenylphosphonium bromide (505 mg) in diethyl ether (9.2 ml) at 0°C was added 1.4 M methyllithium in hexane (0.9 ml). The orange reaction mixture was warmed to room temperature and stirred for 2 hours. To a solution of 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (150 mg) in diethyl ether (10 ml) was added the above obtained 0.13 M wittig reagent at 0°C and warmed to room temperature over 2 hours. The reaction mixture was washed with water and brine, and dried over magnesium sulfate. After evaporation, the residue was purified by silica gel column chromatography followed by chromatography on thin layer chromatography-grade silica gel to give 17-(2-hexenyl)-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (38 mg).

FAB MS : m/z 852 (M + Na)

Example 3-2)

To a cold (0°C), magnetically stirred slurry of benzyltriphenylphosphonium chloride (650 mg) in diethyl ether (10 ml) was added dropwise methyllithium (1.2 ml of 1.4 M in tetrahydrofuran). This ylide solution was allowed to warm to room temperature. A solution of 17-formylmethyl-1-hydroxy-12-[2-(4-hydroxy-3-

methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatircyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (150 mg) in diethyl ether (15 ml) was treated with recooled above ylide solution (1.9 ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for one hour. The mixture was quenched with water and diethyl ether was added thereto. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated. The residue was subjected to a chromatography on silica gel (TLC grade) eluting with 70% ethyl acetate in n-hexane to give 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-(3-phenyl-2-propenyl)-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (70 mg).

FAB MS : m/z 886 (M + Na)

Example 4-1)

A solution of 17-(2-hexenyl)-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (32 mg) in ethanol (2 ml) was admixed with Rhodium on alumina powder (10 mg) and stirred for 3.3 hours under atmospheric pressure of hydrogen. The catalyst was separated by filtration through Celite. Concentration of this filtrate gave 17-hexyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (25 mg).

FAB MS : m/z 827 (M + Na)

Example 4-2)

1-Hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-

17-[3-(phenyl)propyl]-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was obtained in 57.6% yield in substantially the same manner as that of Example 4-1).

FAB MS : m/z 888 (M + Na)

Example 5

17-(2-Butenyl)-1-hydroxy-12-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was obtained in 22.5% yield in substantially the same manner as those of Examples 2 and 3-1) by using butyllithium instead of methyllithium.

FAB MS : m/z 824 (M + Na)

Example 6

17-Butyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclo-hexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was obtained in 80.8% yield in substantially the same manner as that of Example 4-1).

FAB MS : m/z 827 (M + Na)

Example 7

A solution of 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (2.0 g) in tetrahydrofuran (30 ml) and water (1 ml) was treated with catalytic amount of osmium tetroxide in tetrahydrofuran and 4-methylmorpholine N-oxide (873 mg) and stirring was continued for 2 hours at room temperature. Then 4-methylmorpholine N-oxide (583 mg) was added and this mixture was stirred for additional 4 hours at the same temperature. To this reaction mixture

was added diethyl ether and water, and the separated aqueous phase was extracted with diethyl ether. The combined organic layer was washed in turn with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (elution with ethyl acetate) to give pure 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (1.4 g).

FAB MS : m/z 860 (M + Na)

Example 8

17-Formylmethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was obtained in quantitative yield in substantially the same manner as that of Example 2.

^{1}H NMR ($CDCl_3$, δ) : 9.70-9.78 (1H, m)

Example 9

17-(2-Butenyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was obtained in 2.4% yield in substantially the same manner as that of Example 3-1).

FAB MS : m/z 840 (M + Na)

Example 10-1)

1,14-Dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-(3-phenyl-2-propenyl)-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was

obtained in 73.1% yield in substantially the same manner as those of Examples 2 and 3-2).

FAB MS : m/z 902 (M + Na)

Example 10-2)

To a solution of 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-17-(2,3-dihydroxypropyl)-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg) in benzene (5 ml) was added lead tetraacetate (53 mg). The mixture was stirred at room temperature for 1 hour. Methyl (triphenylphosphoranylidene)acetate (120 mg) was added thereto and the stirring was continued for additional 16 hours. Diethyl ether and water were added threto and the organic layer was separated. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The residue was subjected to a silica gel column chromatography eluting with diethyl ether to give 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-(3-methoxycarbonyl-2-propenyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (140 mg).

FAB MS : m/z 884 (M + Na).

Example 11-1)

1,14-Dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-[3-(phenyl)propyl]-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone was obtained in 40.2% yield in substantially the same manner as that of Example 4-1).

FAB MS : m/z 904 (M + Na)

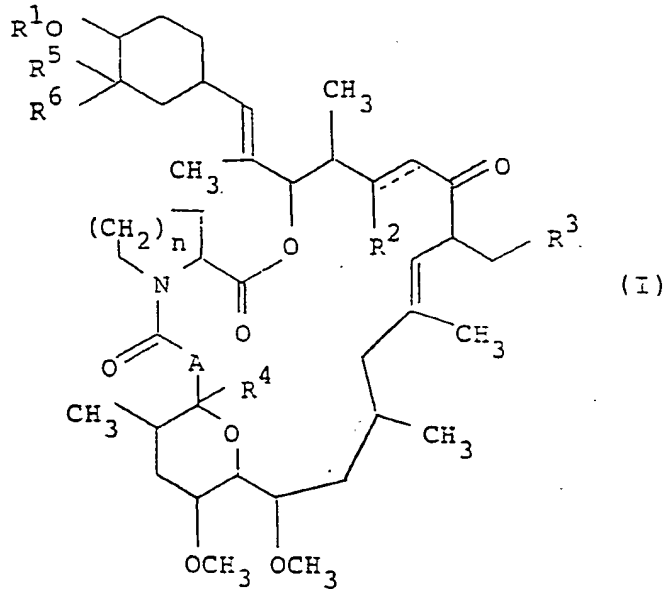
Example 11-2)

A solution of 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-(3-methoxycarbonyl-2-propenyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-one-2,3,10,16-tetraone (120 mg) in methanol (3 ml) was admixed with platinum oxide and stirred for one hour under atmospheric pressure of hydrogen. The catalyst was separated by filtration through Celite. The filtrate was concentrated, and the residue was purified by thin layer chromatography to give 1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-17-[3-(methoxycarbonyl)propyl]-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (10 mg).

FAB MS : m/z 886 (M + Na)

CLAIMS:

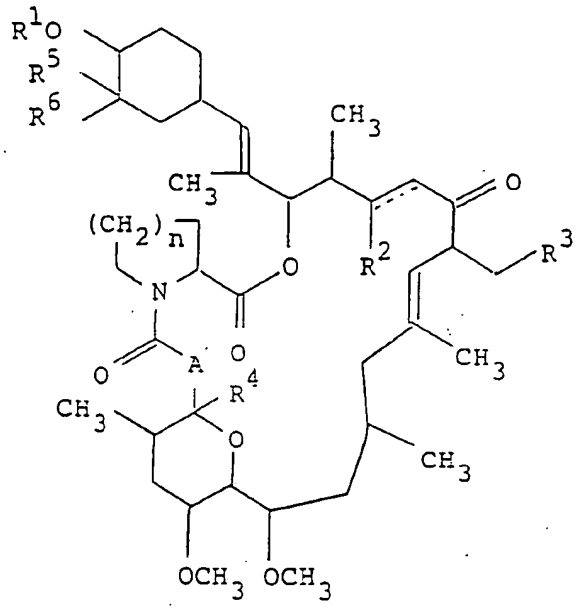
1. A compound of the formula :



(I)

wherein R^1 is hydrogen or acyl,
R^2 is hydrogen, hydroxy, alkoxy or acyloxy,
R^3 is (C_3-C_7)alkyl, aryl(C_2-C_7)alkyl, protected carboxy(C_2-C_7)alkyl, 1-(C_3-C_7)alkenyl, aryl-1-(C_2-C_7)alkenyl or protected carboxy-1-(C_2-C_7)alkenyl,
R^4 is hydroxy or alkoxy,
R^5 is hydrogen and R^6 is hydroxy or methoxy, or
R^5 and R^6 are combined to form oxo,
A is methylene, hydroxymethylene or carbonyl,
n is an integer of 1 or 2, and
the symbol of a line and dotted line is a single bond or a double bond,
or a pharmaceutically acceptable salt thereof.

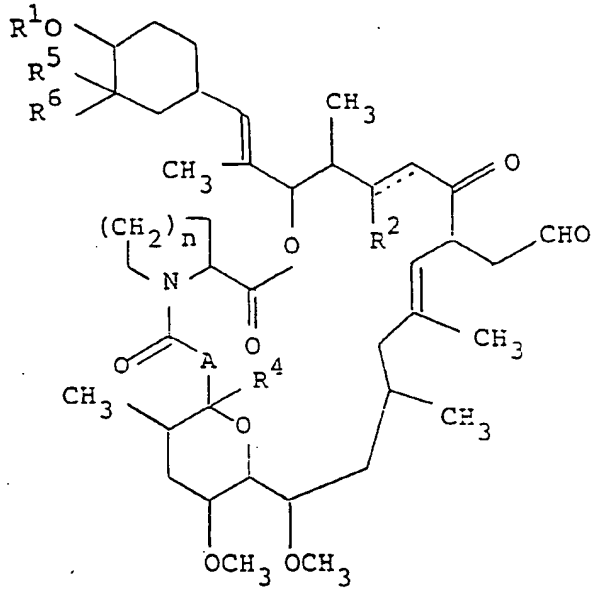
2. A process for the preparation of a compound of the formula :



(I)

wherein R^1 is hydrogen or acyl,
R^2 is hydrogen, hydroxy, alkoxy or acyloxy,
R^3 is (C_3-C_7)alkyl, aryl(C_2-C_7)alkyl, protected carboxy(C_2-C_7)alkyl, 1-(C_3-C_7)alkenyl, aryl-1-(C_2-C_7)alkenyl or protected carboxy-1-(C_2-C_7)alkenyl,
R^4 is hydroxy or alkoxy,
R^5 is hydrogen and R^6 is hydroxy or methoxy, or
R^5 and R^6 are combined to form oxo,
A is methylene, hydroxymethylene or carbonyl,
n is an integer of 1 or 2, and
the symbol of a line and dotted line is a single bond or a double bond,
or a salt thereof, which comprises

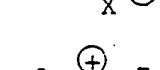
(a) reacting a compound of the formula :



(Ib)

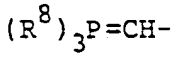
wherein R^1, R^2, R^4, R^5, R^6, A, n and the symbol of a line and dotted line are each as defined above,

or a salt thereof, with a compound of the formula :



(IIIa)

or



(IIIb)

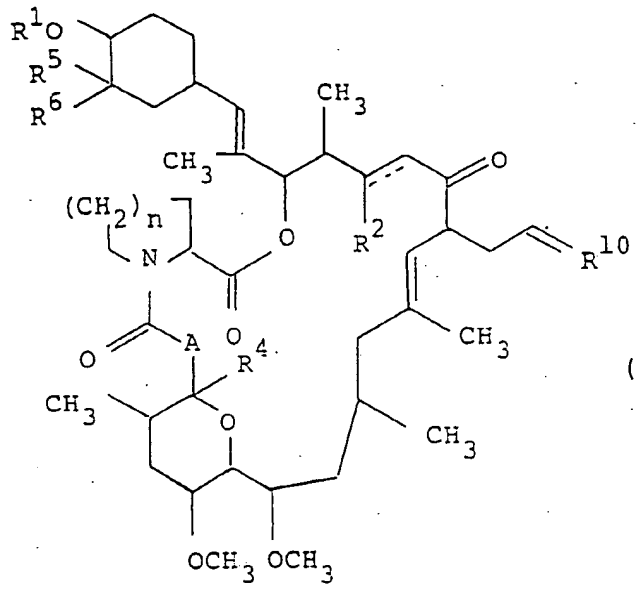
wherein R^7 is (C_2-C_6)alkyl, aryl(C_1-C_6)alkyl or protected carboxy(C_1-C_6)alkyl,

R^8 is aryl,

R^9 is protected carboxy, and

X is halogen,

to give a compound of the formula :



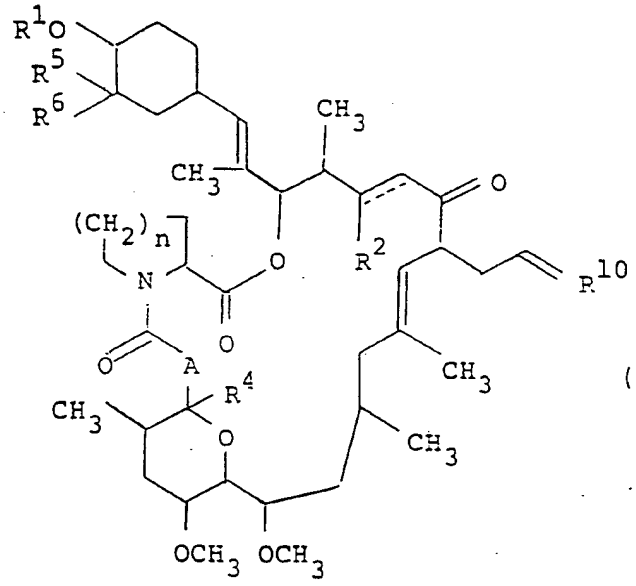
(Ic)

wherein R^1, R^2, R^4, R^5, R^6, A, n and the symbol of a line and dotted line are each as defined above, and

R^{10} is (C_2-C_6)alkylidene, aryl(C_1-C_6)-alkylidene or protected carboxy(C_1-C_6)alkylidene,

or a salt thereof; or

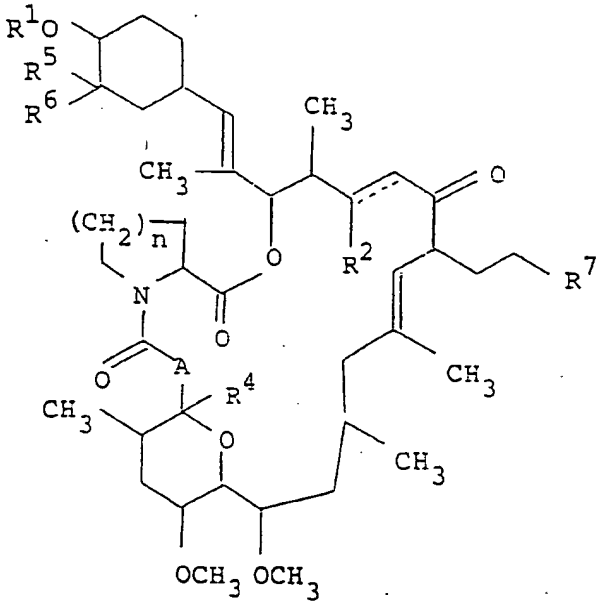
(b) reducing a compound of the formula :



(Ic)

wherein R^1, R^2, R^4, R^5, R^6, R^{10}, A, n and the symbol of a line and dotted line are each as defined above,

or a salt thereof, to give a compound of the formula:



(Id)

wherein R^1, R^2, R^4, R^5, R^6, R^7, A, n and the symbol of a line and dotted line are each as defined above,
or a salt thereof.

3. A pharmaceutical composition containing tricyclo compounds of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. A use of tricyclo compounds of claim 1 as a medicament.

5. A method for treating or preventing resistance by transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases which comprises administering a compound of claim 1 to human or animal.

6. A tricyclo compounds of Claim 1 for use as a medicament.

7. A use of a tricyclo compound of Claim 1 for manufacturing a medicament for treating or preventing resistance by transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases.

8. A process for preparing a pharmaceutical composition which comprises admixing a tricyclo compound of Claim 1 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 91/00811

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 H 19/01 A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 H 19/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP-A-0 184 162 (FUJISAWA PHARMACEUTICAL CO., LTD) 11 June 1986, see pages 100-110 (cited in the application)	1-4,6-8
A	EP-A-0 323 042 (FISONS PLC) 5 July 1989, see pages 18-21, (cited in the application)	1-4,6-8

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-08-1991	19. 09. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1 [X] Claim numbers 5 because they relate to subject matter not required to be searched by this Authority, namely:

Pls. see Rule 39.1(iv) - PCT:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2 [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant s protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9100811

SA 48280

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 13/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0184162	11-06-86	AU-B-	592067	04-01-90
		AU-A-	5059685	12-06-86
		JP-A-	3072483	27-03-91
		JP-A-	3072484	27-03-91
		JP-A-	61148181	05-07-86
		US-A-	4956352	11-09-90
		US-A-	4894366	16-01-90
		US-A-	4929611	29-05-90
EP-A- 0323042	05-07-89	AU-A-	2822889	05-07-89
		EP-A-	0346427	20-12-89
		WO-A-	8905304	15-06-89
		JP-T-	2502463	09-08-90